REZLIDHIA™
(olutasidenib) 150 mg capsules

DOSING AND ADMINISTRATION GUIDE

Information on dosing, administration, and managing potential adverse reactions with REZLIDHIA™ (olutasidenib) capsules

INDICATION

REZLIDHIA is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.

IMPORTANT SAFETY INFORMATION

WARNING: DIFFERENTIATION SYNDROME

Differentiation syndrome, which can be fatal, can occur with REZLIDHIA treatment. Symptoms may include dyspnea, pulmonary infiltrates/pleuropericardial effusion, kidney injury, hypotension, fever, and weight gain. If differentiation syndrome is suspected, withhold REZLIDHIA and initiate treatment with corticosteroids and hemodynamic monitoring until symptom resolution.

Please see additional Important Safety Information throughout and accompanying Full Prescribing Information, including Boxed WARNING.

REZLIDHIA DOSING AND MONITORING FOR PATIENTS WITH IDH1+ AML[1]

TWICE DAILY DOSING

- The recommended dose for REZLIDHIA is one 150 mg capsule taken orally twice daily until disease progression or unacceptable toxicity
- Patients should take REZLIDHIA about the same time each day. Do not administer 2 doses within 8 hours

MISSED DOSE GUIDANCE

- If a dose is vomited, do not administer a replacement dose. Wait until the next scheduled dose is due
- If a dose is missed or not taken at the usual time, administer the dose as soon as possible and at least 8 hours prior to the next scheduled dose. Return to the normal schedule the following day

ORAL ADMINISTRATION

- REZLIDHIA should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal
- Advise patients to swallow capsules whole
- Do not break, open, or chew the capsules

≥6 MONTHS OF TREATMENT

- For patients without disease progression or unacceptable toxicity, treat for a minimum of 6 months to allow time for clinical response

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS

Hepatotoxicity

REZLIDHIA can cause hepatotoxicity, presenting as increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased blood alkaline phosphatase and/or elevated bilirubin. Of 153 patients who received REZLIDHIA, hepatotoxicity occurred in 23% of patients; 13% experienced grade 3 or 4 hepatotoxicity. One patient treated with REZLIDHIA in combination with azacitidine in the clinical trial, a combination for which REZLIDHIA is not indicated, died from complications of drug-induced liver injury. The median time to onset of hepatotoxicity was 1.2 months (range: 1 day to 17.5 months) after REZLIDHIA initiation and the median time to resolution was 12 days (range: 1 day to 17 months). The most common hepatotoxicities were elevations of ALT, AST, blood alkaline phosphatase, and blood bilirubin.

Monitor patients frequently for clinical symptoms of hepatic dysfunction such as fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Obtain baseline liver function tests prior to initiation of REZLIDHIA, at least once weekly for the first two months, once every other week for the third month, once in the fourth month, and once every other month for the duration of therapy. If hepatic dysfunction occurs, withhold, reduce, or permanently discontinue REZLIDHIA based on recurrence/severity.

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MONITORING FOR ADVERSE REACTIONS

Assess blood counts and blood chemistries, including liver function tests, prior to initiation of REZLIDHIA and for the duration of therapy.

RECOMMENDED ASSESSMENT SCHEDULE AT TREATMENT INITIATION AND THROUGHOUT THERAPY

Month	Frequency of lab tests
1	At least once weekly
2	At least once weekly
3	Once every other week
4	Once monthly
5+	Once every other month

Manage any abnormalities promptly. Interrupt dosing or reduce dose for toxicities. See section 2.3 of the Full Prescribing Information for specific guidance on dose modifications and recommendations for adverse event management.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Differentiation Syndrome

REZLIDHIA can cause differentiation syndrome. In the clinical trial of REZLIDHIA in patients with relapsed or refractory AML, differentiation syndrome occurred in 16% of patients, with grade 3 or 4 differentiation syndrome occurring in 8% of patients treated, and fatalities in 1% of patients. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal. Symptoms of differentiation syndrome in patients treated with REZLIDHIA included leukocytosis, dyspnea, pulmonary infiltrates/pleuropericardial effusion, kidney injury, fever, edema, pyrexia, and weight gain. Of the 25 patients who experienced differentiation syndrome, 19 (76%) recovered after treatment or after dose interruption of REZLIDHIA. Differentiation syndrome occurred as early as 1 day and up to 18 months after REZLIDHIA initiation and has been observed with or without concomitant leukocytosis.

If differentiation syndrome is suspected, temporarily withhold REZLIDHIA and initiate systemic corticosteroids (e.g., dexamethasone 10 mg IV every 12 hours) for a minimum of 3 days and until resolution of signs and symptoms. If concomitant leukocytosis is observed, initiate treatment with hydroxyurea, as clinically indicated. Taper corticosteroids and hydroxyurea after resolution of symptoms. Differentiation syndrome may recur with premature discontinuation of corticosteroids and/or hydroxyurea treatment. Institute supportive measures and hemodynamic monitoring until improvement; withhold dose of REZLIDHIA and consider dose reduction based on recurrence.

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RECOMMENDED DOSAGE MODIFICATIONS

ADVERSE REACTIONS	RECOMMENDED ACTION
Differentiation Syndrome	• If differentiation syndrome is suspected, withhold REZLIDHIA until signs and symptoms improve • Administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days • Resume REZLIDHIA at 150 mg twice daily after resolution of differentiation syndrome • If a recurrence of differentiation syndrome is suspected, withhold REZLIDHIA and institute treatment per above guidance. After resolution of symptoms, REZLIDHIA may be resumed at a reduced dose of 150 mg once daily for a minimum of 7 days, after which it can be increased to 150 mg twice daily
Noninfectious leukocytosis	• Initiate treatment with hydroxyurea, as per standard practices. Taper hydroxyurea only after leukocytosis improves or resolves
Grade 3* hepatotoxicity	• Withhold REZLIDHIA and monitor liver function tests, twice per week, until laboratory values have returned to baseline or grade 1* toxicity • Resume REZLIDHIA at a reduced dose of 150 mg once daily and continue monitoring; may increase to 150 mg twice daily if hepatotoxicity resolves to baseline for at least 28 days • If hepatotoxicity (grade 3) recurs at 150 mg once daily, discontinue REZLIDHIA
Grade 4* hepatotoxicity or AST or ALT >3x ULN and total bilirubin >2x ULN and alkaline phosphatase <2x ULN in the absence of a clear alternative explanation	• Permanently discontinue REZLIDHIA
Other grade 3* or higher toxicity considered related to treatment	• Interrupt REZLIDHIA until toxicity resolves to grade 2* or lower • Resume REZLIDHIA at 150 mg once daily; may increase to 150 mg twice daily if toxicities resolve to grade 1* or lower for at least 1 week • If grade 3* or higher toxicity recurs at 150 mg once daily, discontinue REZLIDHIA

*Grade 1 is mild, grade 2 is moderate, grade 3 is severe, grade 4 is life threatening. Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03).

Advise your patients to notify you right away about any adverse reactions they may be experiencing with REZLIDHIA.

DRUG INTERACTIONS

EFFECTS OF OTHER DRUGS ON REZLIDHIA

Strong or Moderate CYP3A Inducers

- Avoid concomitant use of REZLIDHIA with strong or moderate CYP3A inducers
- REZLIDHIA is a CYP3A substrate. Concomitant use of REZLIDHIA with a strong CYP3A inducer decreases olutasidenib Cmax and AUC, which may reduce REZLIDHIA efficacy
- Concomitant use of REZLIDHIA with a moderate CYP3A inducer may also decrease olutasidenib Cmax and AUC, which may also reduce REZLIDHIA efficacy, based on observations from concomitant use with a strong CYP3A inducer

EFFECTS OF REZLIDHIA ON OTHER DRUGS

Sensitive CYP3A Substrates

- Avoid concomitant use of REZLIDHIA with sensitive CYP3A substrates unless otherwise instructed in the substrates prescribing information. If concomitant use is unavoidable, monitor patients for loss of therapeutic effect of these drugs
- REZLIDHIA induces CYP3A. Concomitant use of REZLIDHIA may decrease plasma concentrations of sensitive CYP3A substrates, which may reduce the substrate's efficacy

HOW SUPPLIED

REZLIDHIA 150 mg capsule: white hard gelatin capsule with black ink imprint "OLU 150," available in 30-count bottles of 150 mg capsules (NDC 71332-005-01)

IMPORTANT SAFETY INFORMATION (CONT'D)

ADVERSE REACTIONS

The most common (>20%) adverse reactions, including laboratory abnormalities, were aspartate aminotransferase increased, alanine aminotransferase increased, potassium decreased, sodium decreased, alkaline phosphatase increased, nausea, creatinine increased, fatigue/malaise, arthralgia, constipation, lymphocytes increased, bilirubin increased, leukocytosis, uric acid increased, dyspnea, pyrexia, rash, lipase increased, mucositis, diarrhea and transaminitis.

GERIATRIC USE

No overall differences in effectiveness were observed between patients 65 years and older and younger patients. Compared to patients younger than 65 years of age, an increase in incidence of hepatotoxicity and hypertension was observed in patients ≥65 years of age.

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REZLIDHIA DOSING FOR YOUR ADULT PATIENTS WITH IDH1+ AML[1]

- **150 mg twice daily** at approximately the same time every day
  - Do not administer 2 doses within 8 hours
- **Taken orally on an empty stomach** at least 1 hour before or 2 hours after a meal
  - Swallow capsules whole. Do not break, open, or chew the capsules
- **Treat for at least 6 months** for patients without disease progression or unacceptable toxicity to allow time for clinical response

Not actual size.

For additional information and practice resources, visit REZLIDHIAhcp.com.

IMPORTANT SAFETY INFORMATION (CONT'D)

LACTATION

Advise women not to breastfeed during treatment with REZLIDHIA and for 2 weeks after the last dose.

HEPATIC IMPAIRMENT

In patients with mild or moderate hepatic impairment, closely monitor for increased probability of differentiation syndrome.

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Reference: 1. REZLIDHIA™ [package insert] South San Francisco, CA: Rigel Pharmaceuticals, Inc.

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